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**Lymphoid priming in human bone marrow begins before expression of CD10 with upregulation of L-selectin.**

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**Public Summary:**

Throughout life, the cells of the immune system (i.e. T cells, B cells and Natural Killer/NK cells) are all generated from hematopoietic ("blood-forming) stem cells in the bone marrow through a complex series of differentiation steps. The cells that are generated during first few stages of this differentiation process are called lymphoid progenitors. In order to understand how the immune system is created from stem cells, it is necessary to isolate these rare lymphoid progenitors from the bone marrow. Until this current work, investigators had assumed that the first stage of lymphoid differentiation could be defined based on the presence of a cell surface protein called CD10 on progenitors. However, the CD10-expressing progenitors mainly produce B cells and have relatively little ability to generate T cells and NK cells. In our work, we found that an even earlier type of lymphoid progenitor that does not express CD10 can be found in the human bone marrow. This so-called "lymphoid-primed multipotent progenitor" can be isolated based on expression of a homing molecule called L selectin. We isolated the Lselectin+ cells from human bone marrow and compared their cell growth and gene expression to hematopoietic stem cells and to CD10 expressing progenitors. The Lselectin+ cells showed greater T cell and NK cell potential and equivalent B cell potential compared to CD10+ progenitors. Lselectin progenitors expressed genes in patterns similar to hematopoietic stem cells but have little in common with the CD10+ progenitors, suggesting that the Lselectin+ cells are close relatives to stem cells and represent the earliest stage of differentiation of the adult human immune system yet described.

**Scientific Abstract:**

Expression of the cell-surface antigen CD10 has long been used to define the lymphoid commitment of human cells. Here we report a unique lymphoid-primed population in human bone marrow that was generated from hematopoietic stem cells (HSCs) before onset of the expression of CD10 and commitment to the B cell lineage. We identified this subset by high expression of the homing molecule L-selectin (CD62L). CD10(-)CD62L(hi) progenitors had full lymphoid and monocytic potential but lacked erythroid potential. Gene-expression profiling placed the CD10(-)CD62L(hi) population at an intermediate stage of differentiation between HSCs and lineage-negative (Lin(-)) CD34(+)CD10(+) progenitors. CD62L was expressed on immature thymocytes, and its ligands were expressed at the cortico-medullary junction of the thymus, which suggested a possible role for this molecule in homing to the thymus. Our studies identify the earliest stage of lymphoid priming in human bone marrow.

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